Scientific Abstract:

CEA is overexpressed in virtually all adenocarcinomas of the colon and rectum, and is present on most adenocarcinomas of the breast, lung, pancreas and other regions of the GI tract. The development of an effective immunologic therapy directed towards CEA would have dramatic, widespread therapeutic implications. A recent phase I clinical trial utilizing the first generation of CEA-based vaccines, a recombinant vaccinia virus containing the CEA gene (rV-CEA), demonstrated that CEA-specific T-cell responses could be generated in humans. Similar to rV-CEA, ALVAC-CEA demonstrated a moderate but statistically significant increase in the number of CEA-specific CTL precursors in 7 of 9 patients treated with ALVAC-CEA, and multiple vaccinations boosted the immune response with each treatment. These vaccine trials demonstrated safety in patients with advanced carcinomas, however failed to demonstrate true objective anticancer effects. The extent of the primary response of T cells is paramount to a successful immune response to antigen. At least three distinct "co-stimulatory" molecules normally found on the surface of professional APCs have been reported as capable of providing a signal critical for T-cell activation. Two multigene constructs using retroviral vectors have been synthesized to properly engage the T cell receptor and co-stimulatory receptor, these are Fowlpox-CEA(6D)-B7.1/ICAM/LFA-3 (rF-CEA(6D)-TRICOM) and vaccinia-CEA(6D)-B7.1/ICAM/LFA-3 (rV-CEA(6D)-TRICOM). Pre-clinical studies using these agents have demonstrated significant superiority over constructs without the co-stimulatory molecules, including multiple examples of anecdotal clinical benefit and a few clinical responses. Additionally, preliminary data demonstrates that the mutation in CAP-1 termed CAP1-6D apppears significantly more active in stimulating the immune response when compared to the native CEA peptide. Early results from an ongoing Phase I trial demonstrate that utilization of these multigene construct CEA-based vaccines are likely providing a statistically significant antitumor response in patients, while producing minimal toxicity. This pilot study adds Docetaxel chemotherapy to this vaccine regimen, as a potential immune modulator that may further improve upon the immune response.